ORIGINAL ARTICLE EPIDEMIOLOGY

Secular trends in antibiotic consumption in the adult population in Emilia-Romagna, Italy, 2003–2009

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Abstract

Antibiotic resistance is closely related to antibiotic use and Italy is a country with high levels of both antibiotic use and antimicrobial resistance. We analysed the trend in antibiotic use in the community among adults (≥15 years) and elderly, in the period 2003–2009, in Emilia-Romagna, Italy, a region with over 4 000 000 inhabitants. Data regarding antibiotic use were obtained from the regional public health system databases. Between 2003 and 2009 the antibiotic consumption increased from 15.4 to 18.7 defined daily doses/1000 inhabitants per day (DID) (+21.4%, p <0.0001). The prescription rate in 2009 was 2.19 prescriptions/1000 inhabitants per day, an increase of 13.8% compared with 2003. The highest increase in antibiotic use was observed among persons aged 20–59 years (+24.7%). The proportion of inhabitants receiving at least one antibiotic treatment was 36.4% in 2003 and 39.7% in 2009, and the proportions receiving at least three antibiotic treatments were 3.5% and 4.2%, respectively. The H1N1 pandemic was associated, in October and November 2009, with a 37–90% increase in antibiotic use among the 15–19-year and 20–59-year age groups compared with 2007 and 2008. No other difference was observed in any other age group. The analysis per antibiotic class showed increases for penicillin + beta-lactamase inhibitor (from 3.6 to 6.3 DID), quinolones (from 2.6 to 3.0 DID) and macrolides (from 3.1 to 3.7 DID), whereas cephalosporin use was stable (1.4 DID). A steady increase in antibiotic use in the adult population has been observed in the Emilia-Romagna: public health interventions are mandatory to counteract this trend.

Keywords: Antibiotic class, antibiotic consumption, defined daily dose, Italy, prescription, treatment
Original Submission: 2 November 2010; **Revised Submission:** 13 February 2011; **Accepted:** 16 February 2011
Editor: M. Paul
Article published online: 14 March 2011
Clin Microbiol Infect 2011; **17:** 1698–1703
10.1111/j.1469-0691.2011.03500.x

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Introduction

Bacteria are probably the most adaptable organisms on earth [1]. The use of antibiotics is closely related to the selection of resistance, which is considered an emerging threat [2,3]. This problem, which has reached the lay public [4], is complicated by the limited numbers of new antibiotic agents registered in the last decade and of those that are in the industries' pipelines for the next decade [5]. Antibiotic resistance, a natural event that is estimated to be at least 2 billion years old [6], will be a problem to face for many years to come, possibly forever, unless strategies other than antibiotic use become widely employed to fight bacterial infections.

Antibiotic over-prescription, a common problem, is closely related to resistance [7–9], although antibiotic use alone does not explain all the aspects of resistance induction [10]. The majority of antibiotics are prescribed in the community to treat mild to medium severity infections, in Italy over 85% [11]. Programmes to control antibiotic use have therefore to be implemented in this setting, focusing both on the indications for treatment and antibiotic class selection [12]. Antibiotic use should aim for the most favourable outcome in the individual patient as well as for the minimization of antimicrobial resistance [13].

Italy is among the top antibiotic user in Europe with over 25 defined daily doses per 1000 inhabitants per day (DID), over twice that of the Netherlands [14]. Nonetheless even

in these 'low-antibiotic-use' countries a proportion of the antibiotic prescriptions is inadequate [15].

The aim of this study was to analyse the trends in antibiotic prescription in the community in Emilia-Romagna, Italy between 2003 and 2009 among the adult population, aged ≥15 years; in the Italian health system, this is carried out by the general practitioner.

Methods

Setting and study population

The study was performed in Emilia-Romagna, in northern Italy, which has a population of over 4 million inhabitants, with an average income in 2007 of € 32 802 per year [16], higher than the European average of € 23 600. The average yearly general healthcare expense in the region in 2008 was € 1829 per inhabitant [17]. Antibiotics accounted for 7.9% of the total pharmaceutical costs and represent the fourth leading drug expense in the community setting in the region, the ninth in the country [18,19]. The age of the population remained stable throughout the study period (mean 45.4–45.5 years).

Antibiotic consumption data

Antibiotics in Italy have to be prescribed by a physician, and are not available as over-the-counter drugs. The majority of antibiotics, i.e. >95%, are distributed from the National Health Service free of charge for the patient, or with a minimal charge (€ 1). Data on antibiotic prescriptions at the patient level were obtained from the regional outpatient antibiotic database (Assistenza Farmaceutica Territoriale). Data are recorded using the Anatomic Therapeutical Chemical Classification of the World Health Organization Collaborating Centre [20]. Demographic data were obtained from the regional health service demographic database. A unique patient identifier is available in each database, permitting connection of the different data sets.

The following parameters were evaluated: (i) prescription: number of prescriptions of a certain drug, with a limit of two packages of the same drug per prescription; (ii) treatment: one or more prescriptions, repeated at intervals of <10 days between one prescription and the following one. Each treatment may contain one or more prescriptions.

We considered only the population that is cared for by the family doctors, i.e. ≥15 years old. Children up to 15 years of age are followed by paediatricians. Our analysis took into account a total number of defined daily doses increasing from 20 507 825 in 2003 to 25 359 017 in 2009, and representing 88.3–90.1% of antibiotics distributed in the community setting.

Monthly analysis of antibiotic prescribing

To evaluate the effect of the influenza pandemics on antibiotic prescriptions, in particular the 2009 H1N1 pandemic, we analysed the monthly antibiotic prescribing, expressed as number of antibiotic treatments per 1000 persons, stratified by age group. This analysis was performed for the last 3 years of the study period: 2007–2009.

Statistical analysis

The antibiotic consumption was analysed through different parameters: (1) population exposed to antibiotics, expressed as: (1a) the total number of inhabitants receiving at least one and those receiving at least three antibiotic treatments; (1b) the number of patients treated per 1000 inhabitants per day; (2) total consumption: (2a) defined daily dose per 1000 inhabitants per day (DID) [17]; (2b) prescriptions per 1000 inhabitants per day; 2c) treatments per 1000 inhabitants per day. These data were stratified for antibiotic class and age group (15–19, 20–59, 60–79 and ≥80 years). The DID was calculated for each of the 11 regional healthcare agencies. To evaluate DID trends, the Poisson regression model was applied to yearly consumption rates on the complete data set. No change in antibiotic packaging was observed over the study period.

Analyses were performed using SAS version 9.1 (SAS Institute, http://www.sas.com/technologies/analytics/statistics). All statistical tests were two-tailed; a p value of <0.05 was considered significant.

Results

During the study period, the overall antibiotic consumption in the adult population (≥15 years old) in Emilia-Romagna increased from 15.4 DID in 2003 to 18.7 in 2009 (+21.4%; p <0.0001) (see Fig. 1). Similarly, both the prescription and treatment rates increased, respectively, from 1.92 to 2.19 prescriptions per 1000 inhabitants per day (+13.8%) and from 1.68 to 1.91 (+13.2%). The number of patients treated per 1000 inhabitants per day passed from 1.00 in 2003 to 1.09 in 2009 (+9%).

The highest antibiotic use was observed in the elderly (≥80 years old) (see Fig. 1), and the highest increase in antibiotic use was seen among the population aged 20–59 (+24.7%). Men received overall about 14% less antibiotics than women, although differences were observed among age groups. Whereas young (age 15–19 years) and aged (60–79 years) men and women had similar antibiotic use,

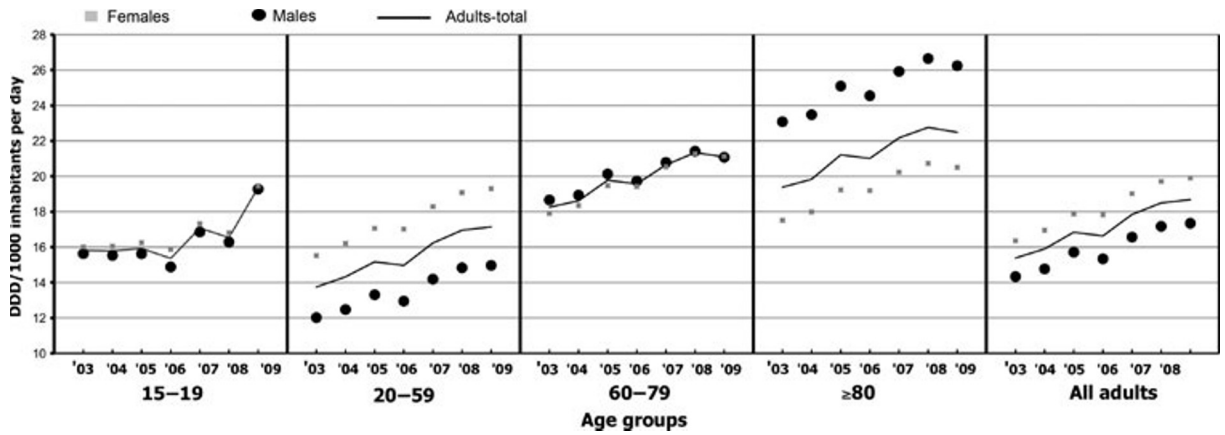

FIG. 1. Antibiotic consumption expressed in defined daily doses (DDD)/1000 inhabitants per day, in the adult population, divided by gender, Emilia-Romagna 2003–2009.

men aged 20–59 years received around 30% less antibiotics than similarly aged women because of the higher frequency of uncomplicated urinary tract infections in fertile women. Conversely, men aged ≥80 years were prescribed about 20% more antibiotics than similarly aged women, because of a higher frequency of respiratory tract infections and worse general health (see Fig. 1). These differences between genders remained stable over the years.

The proportions of adults receiving at least one or three or more antibiotic treatments were 36.4% and 3.5% in 2003 and increased steadily though 2009 to 39.7% (+9.1%) and 4.2% (+14.3%), respectively.

The analysis of the prescriptions per month of the year for the period 2007–2009 showed a 41–90% increase in antibiotic use in the age group 15–19 years, for October and November 2009, during the peak of the H1N1 pandemic, compared with the same months during 2007 and 2008 (see Fig. 2). A milder increase (37%) was observed in the age group 20–59 years between November 2009 and 2008, only. Antibiotic use returned to baseline levels in December 2009. No other difference in antibiotic consumption was observed in any other age group.

Penicillins were the most prescribed antibiotic class throughout the study period and their use increased steadily from 7.1 to 9.5 DID. This increase was mainly the result of the rise in prescription of penicillin + beta-lactamase inhibitor (PBLI) combinations, rising by 75%, from 3.6 to 6.3 DID. A substantial increase was observed also for quinolones (25%) and macrolides (19%), whereas cephalosporins remained stable around 1.4 DID (−3%) (see Table 1).

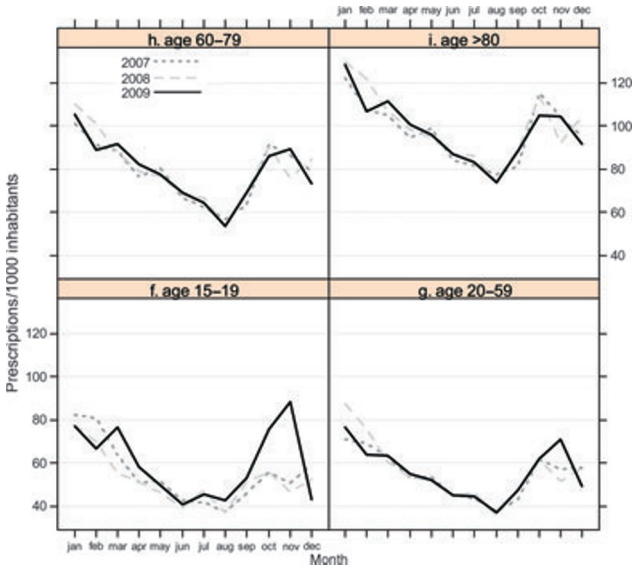

FIG. 2. Proportion of people who were prescribed an antibiotic treatment, per month, divided by age group, Emilia-Romagna 2007–2009.

TABLE 1. Antibiotic consumption expressed as defined daily doses (DDD)/1000 person days, Emilia-Romagna 2003–2009

		DDD/1000 inhabitant-days						
ATC code	**Antibiotic class**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
J01CR	Penicillin + beta-lactamase inhibitor	3.6	4.0	4.3	4.5	5.3	5.9	6.3
J01CA	Penicillins with extended spectrum	3.5	3.6	3.7	3.5	3.5	3.5	3.2
J01FA	Macrolides	3.1	3.2	3.3	3.2	3.4	3.6	3.7
J01M	Quinolones	2.6	2.7	3.0	3.1	3.2	3.2	3.1
J01DB, J01DC, J01DD, J01DE	Cephalosporins	1.4	1.4	1.5	1.4	1.4	1.4	1.4
J01EE01	Trimethoprim + sulfamethoxazole	0.4	0.4	0.4	0.4	0.3	0.3	0.3
J01XX01	Fosfomycin	0.3	0.3	0.3	0.3	0.3	0.3	0.3
	Other	0.3	0.3	0.3	0.3	0.3	0.4	0.4

ATC, Anatomic Therapeutical Chemical Classification of the World Health Organization Collaborating Centre.

Substantial differences were observed among the 11 health agencies of the region: the antibiotic consumption varied between 15.3 and 18.1 DID in 2003 and between 18.3 and 21.0 in 2008, with the relative increase ranging between 6.0% and 20.0%. Significant differences in antibiotic prescription habits and trends were observed among local health agencies, particularly regarding the use of wide-spectrum penicillins (WSP), i.e. amoxicillin and ampicillin, and PBLI. Use of PBLI in 2009 varied in the different local agencies between 1.95 and 3.28 DID, with relative increases of 56–106%, compared with 2003. Three different patterns of penicillin use were identified: (i) wide prevalence of PBLI with a PBLI : WSP ratio >2, in no agency during 2003 and in five agencies in 2009; (ii) mild prevalence of PBLI use with PBLI : WSP ratio between 1 and 2, in six agencies, but not the same ones, both in 2003 and 2009; and finally, (iii) low prevalence of WSP, with a PBLI : WSP <1, in five agencies in 2003 but none in 2009.

Quinolone use increased between 2003 and 2009, by 5–42%, from 2.04–2.81 to 2.42–3.52 DID. Similarly, macrolide use increased by 0.27–1.17 DID (8–48%). The use of cephalosporins changed differently in the different areas, ranging from a 29% decrease to a 22% increase.

Discussion

This analysis shows that antibiotic use in the adults residing in Emilia-Romagna, Italy, is high, almost 20 DID, and that between 2003 and 2009 there was a stable trend toward an increase, at a rate of about 0.67 DID or 3%, per year. Furthermore, over the last few years there has been a significant drift in the type of antibiotic prescribed, with an increase in the use of PBLI, macrolides and quinolones, and a reduction in the proportion, but not in the overall use, of cephalosporins. The analysis, performed at the single healthcare agency level, showed that there are differences in antibiotic prescription habits even within the same region, with variations of up to 2.7 DID, i.e. 15%; these are even more evident when analysed at substance level. Striking dissimilarities between neighbouring areas in the use of WSP compared with PBLI were observed.

Despite this high antibiotic consumption rate Emilia-Romagna is performing better than the national average of 25.1 DID in 2008 [18]. Wide variations are observed within the country, ranging from 16.1 DID in the province of Bolzano to 34.9 DID in Sicily and 39.9 DID in Campania, with national trends towards an increase. This constant trend toward an increase in antibiotic use is worrying and indicates that a public health intervention to control antibiotic use is imperative. This trend has been observed despite the lack of evident factors, such as an increase in morbidity or mortality among the population, or significant bacterial outbreaks and epidemics, i.e. involving >100 inhabitants, being reported by the regional alert system [21], with the exception of the H1N1 pandemic. Furthermore, because of the limited number of new antibiotics registered for community-acquired infections in this time, no strong marketing pressure was observed from the pharmaceutical industry. On the other hand, some commonly prescribed antibiotics, such as co-amoxiclavulate or ceftriaxone, became generics. The loss of patent of these and other antibiotics may represent a confounding factor because the national and regional antibiotic expenditure is decreasing, despite an increase in antibiotic use, making public health interventions on antibiotics less impellent to the administrators [18].

Most importantly a constant trend toward an increase in antibiotic resistance particularly regarding *Enterobacteriaceae* has been observed within our region. Among *Escherichia coli* isolates the proportion of third-generation cephalosporin-resistance in blood isolates rose from 4.7 to 22.9% between 2003 and 2009. Similar antibiotic resistance trends have been observed among other *Enterobacteriaceae*, particularly *Klebsiella pneumoniae*. In contrast, both methicillin-resistance rates among *Staphylococcus aureus* isolates and

ceftazidime-resistance among *Pseudomonas aeruginosa* strains remained stable around 40% and 30%, respectively [11].

The rising trend observed in our region is similar to what has been reported in other countries where no intervention by the public health sector aimed at controlling antibiotic use has been performed, such as Ireland or Israel [22]. Although a possible explanation of this trend in antibiotic over-prescription may be related to cultural and communication problems, both at the doctor and the population levels, as already identified in the paediatric population by our group [23], it is well known that different strategies to control antibiotic consumption, including pamphlets and posters, print media, billboards, radio, television, websites, letters, guidelines, seminars, academic detailing, targeting both the public and the physicians, can be successful [24]. The French antibiotic campaign, launched in 2001 and based on the slogan *Les antibiotiques, c'est pas automatique* (Antibiotic, it is not automatic), is a clear example of how a country with a high antibiotic use can significantly reduce it through a nationwide intervention [25]. As the French experience shows, such an intervention is expensive but may be able to generate large money savings: the total amount of money spent on systemic antimicrobials fell from € 1026 million in 2001 to € 669 million in 2008 (−35%), with a total saving from 2002 through 2008, based upon 2001 expenditures, of € 1.4 billion [26]. Cost-effectiveness of antibiotic-use campaigns has been shown to be good, even investing relatively high amounts of money. The French campaign cost some € 500 million for 6 years, i.e. about € 0.8 per inhabitant per year [27]: the net savings have then been slightly less than € 1 billion. Other campaigns, such as the Belgian one, although still having interesting results, had much lower costs, i.e. € 380 000, or € 0.04 per patient per year [28]. The French per-capita investment would be equivalent, in Italy, to 10–30% of the cost of one single box of a common antibiotic. These amounts are much lower than those dedicated to promoting antibiotic use by the pharmaceutical companies, estimated to be about $ 5 per patient per year [29]. Finally, and probably most importantly, the reduction in antibiotic use has been associated with a reduction in antibiotic resistance [30]. We did not observe any significant change in antibiotic prescriptions after the introduction of European Antibiotic Awareness Day in 2008 nor in 2009, compared with 2007, particularly during the winter season, possibly because of the limited time available for the trend analysis and the H1N1 pandemic.

Our analysis has some limitations, the first and most important being that, based upon International Medical Statistics, the reported data represent a 20% underestimation of the real antibiotic consumption, as previously reported [31]. Furthermore, over the last 3 years, an increasing proportion of antibiotics, in 2009 around 4%, have been distributed directly on discharge from the hospital, representing a second cause of underreporting.

In conclusion, antibiotic use in Emilia-Romagna has steadily increased over the last 7 years. One intervention was implemented in 2010, a regional project on hospital antimicrobial stewardship. Furthermore, a campaign on wise antimicrobial use in the community setting in two provinces is being devised, and will be launched in autumn 2011. While awaiting the results of these interventions, new programmes are necessary, such as regional or national guidelines for common community-acquired infections. We feel that each country or region with a high level of antibiotic consumption should implement a local campaign on antibiotic use, possibly profiting from the European Centres for Disease Control campaign and material, which are freely available on the internet.

Transparency Declaration

No funding nor any conflict of interest may be reported for this study.

References

1. Sykes R. The 2009 Garrod Lecture: the evolution of antimicrobial resistance: a Darwinian perspective. *J Antimicrob Chemother* 2010; 65: 1842–1852.
2. Rossolini GM, Mantengoli E. Antimicrobial resistance in Europe and its potential impact on empirical therapy. *Clin Microbiol Infect* 2008; 14 (Suppl. 6): 2–8.
3. Grundmann H, Aires-de-Sousa M, Boyce J, Tiemersma E. Emergence and resurgence of methicillin-resistant *Staphylococcus aureus* as a public-health threat. *Lancet* 2006; 368: 874–885.
4. Blue L. The end of antibiotics? Time. Aug 16, 2010 http://wellness.blogs.time.com/2010/08/16/the-end-of-antibiotics accessed on 17 August, 2010.
5. Livermore DM. Has the era of untreatable infections arrived? *J Antimicrob Chemother* 2009; 64 (Suppl. 1): i29–i36.
6. Hall BG, Barlow M. Evolution of the serine beta-lactamases: past, present and future. *Drug Resist Updat* 2004; 7 (2): 111–123.
7. Goossens H, Ferech M, Van der Stichele R *et al.* Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; 365: 579–587.
8. Malhotra-Kumar S, Lammens C, Coenen S *et al.* Impact of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci among healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet* 2007; 369: 482–490.
9. Costelloe C, Metcalfe C, Lovering A *et al.* Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010; 340: C2096.
10. van deSande-Bruinsma N, Grundmann H, Verloo D *et al.* Antimicrobial drug use and resistance in Europe. *Emerg Infect Dis* 2008; 14: 1722–1730.

11. Pan A, Buttazzi R, Moro ML. Sorveglianza dell'antibioticoresistenza e uso di antibiotici sistemici in Emilia-Romagna. Rapporto 2008. Area Rischio Infettivo, Agenzia Sanitaria e Sociale Regionale dell'Emilia-Romagna. (Surveillance of antibiotic resistance and systemic antibiotic use in Emilia-Romagna. Report 2008. Infectious Risk Area, Health and Social Regional Agency of Emilia-Romagna) (In Italian) Published December 20, 2010. Available at: http://asr.regione.emilia-romagna.it/wcm/asr/collana_dossier/.
12. Mölstad S, Erntell M, Melander E *et al.* Sustained reduction of antibiotic use and low bacterial resistance: 10-year follow-up of the Swedish Strama programme. *Lancet Infect Dis* 2008; 8: 125–132.
13. Paterson DI, Rice LB. Empirical antibiotic choice for the seriously ill patient: are minimization of selection of resistant organisms and maximization of individual outcome mutually exclusive? *Clin Infect Dis* 2003; 36: 1006–1012.
14. Coenen S, Muller A, Adriaenssens N *et al.* European Surveillance of antimicrobial consumption (ESAC): outpatient parenteral antibiotic treatment in Europe. *J Antimicrob Chemother* 2009; 64: 200–205.
15. Otters HB, van der Wouden JC, Schellevis FG, van Suijlekom-Smit LW, Koes BW. Trends in prescribing antibiotics for children in Dutch general practice. *J Antimicrob Chemother* 2004; 53 (2): 361–366.
16. Istituto nazionale di Statistica (ISTAT). *Condizioni di vita e distribuzione del reddito in Italia. Anno* 2008. (National Institute of Statistics (ISTAT). Live conditions and income distribution in Italy. Year 2008) (In Italian) Published December 29, 2009 http://www.istat.it/salastampa/comunicati/non_calendario/20091229_00/ accessed on 18 August, 2010.
17. Servizio Sanitario Regionale, Emilia Romagna. *Il Servizio sanitario regionale dell'Emilia-Romagna e il nuovo welfare. Le strutture, la spesa, le attività al 31.12.2008, i programmi, i modelli organizzativi.* (Regional Health System, Emilia-Romagna. The regional Health System of Emilia-Romagna and the new welfare. The structures, the expenses, the activities as of December 31 2008, the programs, the organizational models.) (In Italian) Available at: http://www.saluter.it/wcm/saluter/pubblicazioni/ accessed on 18 August, 2010.
18. Gruppo di lavoro OsMed. *L'uso dei farmaci in Italia. Rapporto Nazionale anno 2009*. (OsMED working group. The use of drugs in Italy. National report 2009.) Roma: Il Pensiero Scientifico Editore, 2010. Pages 54–59.
19. Data available with password at http://www.regione.emilia-romagna.it/sisinf/aft/reportistica.htm accessed on October 26, 2010.
20. WHO Collaborating Centre for Drug Statistic Methodology. ATC/DDD Index 2010. Available at: http://www.whocc.no/atc_ddd_index/.
21. Moro ML, Buttazzi R, Marchi M *et al.* Valutazione del nuovo Sistema regionale di segnalazione rapida di eventi epidemici ed eventi sentinella in Emilia-Romagna. Primi due anni di attività (aprile 2006–marzo 2008). Agenzia Sanitaria e Sociale Regionale dell'Emilia Romagna. (Evaluation of the new rapid reporting system of outbreaks and alert conditions in Emilia-Romagna. First 2 years of activity (April 2006–March 2008) Health and Social Regional Agency of Emilia-Romagna) (In Italian). Available at: http://asr.regione.emilia-romagna.it/wcm/asr/aree_di_programma/rischioinfettivo/gr_funz/pr_epidemie/pubblicazioni/report_alert.htm.
22. European Surveillance on Antimicrobial Consumption Interactive database. Available at: http://app.esac.ua.ac.be/esac_idb/consumption/rates.htm accessed on 18 August, 2010.
23. Moro ML, Marchi M, Gagliotti C, Di Mario S, Resi D, "Progetto Bambini e Antibiotici [ProBA]" Regional Group. Why do paediatricians prescribe antibiotics? Results of an Italian regional project *BMC Pediatr* 2009; 9: 69.
24. Huttner B, Goossens H, Verheij T, Harbarth S, on behalf of the CHAMP consortium. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *Lancet Infect Dis* 2010; 10: 17–31.
25. Sabuncu E, David J, Bernède-Bauduin C *et al.* Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002–2007. *PLoS Med* 2009; 6: e1000084.
26. Agence française de sécurité sanitaire des produits de santé. Analyse des ventes de medicaments aux officines et aux hôpitaux en France 1998–2008. 10ème édition. Paris 2010: 55–6 (In French) Available at: http://www.afssaps.fr/Afssaps-media/Publications/Rapports-et-syntheses.
27. Huttner B, Harbarth S. Antibiotics are not automatic anymore – the French national campaign to cut antibiotic overuse. *PLoS Med* 2009; 6: e1000080.
28. Goossens H, Guillemot D, Ferech M *et al.* National campaigns to improve antibiotic use. *Eur J Clin Pharmacol* 2006; 62: 373–379.
29. Ma J, Stafford RS, Cockburn IM, Finkelstein SN. A statistical analysis of the magnitude and composition of drug promotion in the United States in 1998. *Clin Ther* 2003; 25 (5): 1503–1517.
30. European Antimicrobial Resistance Surveillance System. EARSS Annual Report 2008. On-going surveillance of *S. pneumoniae, S. aureus, E. coli, E. faecium, E. faecalis, K. pneumoniae, P. aeruginosa*. Bilthoven, The Netherlands, October 2009: 55–58 http://www.rivm.nl/earss/result/Monitoring_reports/.
31. Gagliotti C, Mazzetti I, Moro ML. Comparison of sales and reimbursement data regarding outpatient antibiotic use in a northern Italian Region. *Pharmacoepidemiol Drug Saf* 2009; 18: 1115–1118.